REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 30-58 will be pending in the application subsequent to entry of this Amendment. Various original claims have been revised and reformatted in order to direct them to statutory subject matter and to address issues raised in at least item 3 of the Official Action. For convenience and organizational purposes the previous claim set has been deleted and new claims 30-58 are presented.

Previous "use of" claim 17 (now new claim 47) has been reformatted as a method claim dependent on new claim 46.

Claims 18 and 20 have been deleted.

Previous "use" claims 19 and 21-27 have been reformatted as new method claims 48-55.

Two new pharmaceutical composition claims have been added as claims 57 and 58. Claim 57 is based on a combination of previous claims 9, 10 and 12. Claim 58 is based on a combination of previous claims 9, 11 and 12.

The main points of the current Official Action relate to general lack of unity of inventive concept (items 1 and 2) as well as claims directed to "more than one species of the generic invention" (*see* items 4 and 5). The crux of the Official Action, which is essentially a requirement for restriction, is based upon an incorrect understanding/assertion that the "independent claim (now claim 30) does not avoid the prior art". Applicants first address this assertion and will explain why the examiner's view is incorrect.

Claim 30 is believed to be inventive over New *et al* and Wong *et al* for the following reasons.

The Examiner asserts that together New *et al* and Wong *et al* render obvious the present invention. In particular, the Examiner alleges that New *et al* provide a composition comprising a mixture of an active principle, aromatic alcohol, and a solubilization agent, while Wong *et al* provide the use of butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA) and analogues thereof. The implication appears to be that combining the teaching of New *et al* and Wong *et al* would therefore lead to a composition as defined in present claim 1. With respect, the applicant disagrees.

New *et al* and Wong *et al* do not teach a composition with all the features of claim 30

Claim 30 requires that a composition of the present invention must contain the aromatic alcohol absorption enhancer in an amount by weight greater than or equal to that of the active macromolecular principle. There is no suggestion whatsoever in Wong *et al* that BHT, BHA and analogues and derivatives thereof could be added to, say, a composition of New *et al* in such a proportion. Further, that doing so might enhance the absorption across a barrier layer of intestinal cells in the instance that the composition contained a macromolecule is not alluded to in any way by Wong *et al*, and so is entirely unexpected.

That is because Wong *et al* specifically teach that butylated hydroxyl toluene and butylated hydroxyl anisole (among others) may be used as antioxidants. As explained at page 2 lines 3-6 of the present application, these compounds have in fact been used for at least twenty years in pharmaceutical preparations, generally as antioxidants. Thus, the section of Wong *et al* which indicates these compounds could be added to their formulations as antioxidants is merely incidental to the "real" teaching of Wong *et al*, which involves a news means for controlling the delivery of liquid active agent formulations (as discussed further below).

As explained at page 2 lines 5-6, despite these compounds having been used in pharmaceutical preparations for years, generally as antioxidants, their ability to act as permeation enhancers has never been appreciated. Thus, Wong *et al* is actually a typical example of the previous known use of these compounds discussed by the applicant at page 2 lines 3-5 of the present application.

Moreover, at column 14 lines 29-47 Wong *et al* provide a "laundry list" of antioxidants said to be suitable for use in their compositions. Even those specifically listed are said to be merely "representative". Also, the antioxidants can be used in any part of the dosage form, i.e. not just in the drug-containing layer. The skilled person could have taken no indication from this section of Wong *et al* that any useful property could be realized for any of the listed antioxidants beyond their usual known antioxidant effect, and that it is immaterial which of the multitude of possible known antioxidants is used.

Furthermore, as explained at page 4 line 34 to page 5 line 8, when these compounds are used as antioxidants (such as by Wong *et al* in US 6,342,249), then they are used at concentrations of up to 0.1 % w/v of the formulation. Evidence for this may be found, for

instance, in the literature reference quoted by the applicant at page 4 line 36 to page 5 line 2 of the present application. Higher concentrations are generally considered to be of no antioxidant benefit (see page 5 lines 2-3). Accordingly, the skilled person would simply not consider using one of the antioxidants listed by Wong *et al* in an amount by weight equal to or greater than that of the macromolecular principle, which is an amount much higher than was previously described in the prior art (see page 5 lines 5-8 of the present application).

This is further reinforced by the examples presented by Wong *et al*. Thus, the preparation of the drug layer described at column 26 lines 38-64 involves the addition of only 0.01 % of an antioxidant (see line 60). Accordingly, it is simply not credible to suggest that the skilled person would, in the light of Wong *et al*, have had any motivation whatsoever to add an antioxidant to a composition of New *et al* in an amount greater than up to 0.1 % w/v of the formulation. On the contrary, even if the skilled person had sought to add an antioxidant, Wong *et al* would have taught him to use less than 0.1 %, because it exemplifies the use of only 0.01 %. Thus, Wong *et al* actually teach away from the idea of using an amount by weight of the BHT, BHA or analogue or derivative thereof which is equal to or greater than the weight of the macromolecular principle.

Even if the skilled person had contemplated using greater amounts of BHT, BHA and their analogues or derivatives (which he would not have done), he would be likely to be discouraged by running into difficulties caused by the poor solubility of these compounds, as explained at page 2 lines 6-12.

It is also of note that, unlike Wong *et al*, the present applicants are concerned only with macromolecules. Wong *et al* discuss how the active component in their compositions can be any of a vast number of agents, for example those listed from column 11 line 32 to column 12 line 62. In view of this, the skilled person would have had no motivation to consider compositions containing only macromolecules. On the contrary, if anything he would have been led by Wong *et al* to consider primarily smaller molecules, in view of the mean pore size of the preferred porous particles described by Wong *et al* (calcium hydrogen phosphate sold under the trademark FujiCalin®) being in the order of 70 Angstroms.

In view of the above comments, if the skilled person had started from New *et al*, then Wong *et al* would not have taught him to use BHT, BHA or an analogue as an antioxidant in the

compositions of New *et al.* Further, he would have had no motivation to use amount by weight of the BHT, BHA or analogue or derivative thereof which is equal to or greater than the weight of the macromolecular principle, as this would have been contrary to the general understanding that such compounds are of no benefit at concentrations above 0.1 %. In fact, based on Wong *et al* he would be more likely to have used an even lower amount of antioxidant. That these compounds can act as permeability enhancers was entirely unexpected in view of the prior art, and even more so with respect to macromolecular principles.

If the skilled person had combined the teachings of New *et al* and Wong *et al*, he would actually have been led away from the composition of claim 30

What would the skilled person actually have done if he had combined the teachings of New *et al* and Wong *et al*? Starting from New *et al*, the skilled person reading Wong *et al* would immediately realize that Wong *et al* are concerned with a new way to affect the controlled delivery of liquid active agent formulations. This is apparent from the introductory section at the very start of the description (column 1 lines 9-10): "the invention pertains to the controlled delivery of pharmaceutical agents and dosage forms therefore". The crux of the invention is outlined from column 2 line 66 to column 3 line 32. Thus, the key contribution to the art made by Wong *et al* is the discovery that certain porous powders can be used to carry liquid active agents formulations. Based on this, they have devised dosage forms containing such porous powders, which enable the controlled release of drugs sorbed within such porous powders. Figures 1-10, as described from column 16 line 19 to column 17 line 33, discuss how their invention works.

Accordingly, if the skilled person had sought to combine the teachings of these two documents as the Examiner has suggested, his first step would surely have been to take the composition described by New *et al*, attempt to store it within a porous powder of the type described by Wong *et al*, and then try to incorporate the powder in a controlled release rate dosage form. Clearly this would only have led the skilled person away from a composition as defined in claim 30.

In view of the above comments, it is respectfully submitted that any suggestion that the composition of claim 30 would have been obvious in view of New *et al* and Wong *et al* can only be based on hindsight, which is not permitted when assessing obviousness. Accordingly, it is

believed that the Examiner should now be able to acknowledge that the invention as defined in the present application is not obvious in view of New *et al* and Wong *et al*. Accordingly, claim 30 provides a unifying inventive concept and so it is believed that the restriction requirements made by the Examiner should be withdrawn and that the present application may now be allowed.

In order to be fully responsive and elect a single claim, applicants elect the subject matter of new claim 57, that is a pharmaceutical composition which falls under Group I in the listing in item 1 of the Official Action. Applicants submit that at least the method of treatment claims also fall within elected subject matter and that claims directed to a method of enhancing the absorption of an active molecular principle, that would be Group III of item 1, also relate to the elected subject matter. In any event, the examiner has already acknowledged an obligation to rejoin claims in item 6 of the Official Action.

Attention is directed to co-pending application Serial No. 10/553,169 filed October 17, 2005 and currently pending in Art Unit 1654 (the same art unit as the present application) before Examiner Christina Bradley. This co-pending application has received an initial examination on the merits and the documents cited in that Official Action are identified in the concurrently filed Information Disclosure Statement filed in the present application. The examiner is requested to take into account the existence of Serial No. 10/553,169 as well as the documents of record in it, namely those documents listed in the concurrently filed Information Disclosure Statement.

Should the examiner require further information or documentation, please contact the undersigned.

Respectfully submitted,

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